Congenital Malformations A Report of a Study of Series of Consecutive Births in 24 Centres

A report is presented of a study of births in 24 centres in 16 countries with respect to the occurrence and type of congenital malformations found in stillborn and liveborn infants. In all, the outcomes of 421 781 pregnancies are investigated (416 695 single births, 5022 sets of twins, 63 sets of triplets, and one set of quadruplets). The frequencies of malformations of specific types or of groups of malformations are considered with particular reference to geographical variations and associations with consanguinity of parents. The evidence relating to clinical and etiological heterogeneity is considered, as well as that on the genetical contribution to congenital malformations and perinatal mortality. The data are presented in considerable detail in tables and in addition there is available on request to the authors a 400-page companion booklet of basic tables for each centre.

Among the findings of particular interest are: the large contribution of neural tube defects to foetal wastage in most countries and the significant correlations of frequencies of these defects over the 24 recording centres; the unexplained correlation in frequency between neural tube defects and dizygous twinning; the marked association of consanguinity of parents with increased stillbirth rates and frequency of early death of the infant, these frequencies being highest where parents are most closely related; and the demonstration that, if malformations known to be due to the expression of single recessive gene mutations are ignored, consanguinity of parents is demonstrably associated in these data with neural tube defect frequencies only.

A number of interesting observations, either novel or confirmatory of views derived from different approaches, emerge in respect of specific groups of malformations. This is so particularly in respect of harelip and cleft palate, malformations of the gut, malformations of the urogenital tract and multiple malformations occurring in the same child. The findings in respect of twin births are of interest for the light which they throw on the relative contributions of monozygous and dizygous pairs to the total variance of twinning frequencies in the different centres. Estimates are made of the effects of monozygosity on survival of infants and of the occurrence of malformations.

1. INTRODUCTION

ORIGINS OF THE STUDY

In 1958, in the course of discussions in which the World Health Organization took part on needs in medical research, a prospective study of congenital malformations in different countries was suggested as an example of an undertaking which it would be difficult to carry out except under the auspices of the Organization. It was further suggested that a simple and unambitious study would be useful in a field where there were big gaps in knowledge and that much useful experience in the methodology of international studies would accrue.

Subsequently, at an informal meeting at Ann Arbor, Michigan, USA, in April 1959, Professor J. V. Neel, Professor W. J. Schull, Dr J. A. Fraser Roberts and Dr A. C. Stevenson considered, at the request of WHO, all the suggestions for genetic research which had been put forward at the 1958 discussions. It was again recommended that a simple prospective study of the malformations occurring in a consecutive series of births in hospitals in several countries should be undertaken. The limitations of such data, inevitably determined by the biasses introduced by recording hospital births only, were fully recognized. It was realized also, however, that in many of the areas where it would be of great interest to have data there was no possibility of getting adequate information about home births.

This recommendation was accepted and one of us (A.C.S.) was asked to organize and carry out the study from the Population Genetics Research Unit of the Medical Research Council of Great Britain,

as facilities were available there for collection and analyses of the not inconsiderable amount of data which would be assembled. Thereafter the authors of this report were responsible for the conduct of the study.

ORGANIZATION AND CONDUCT OF THE STUDY

It was decided that a minimum of about 10 000 consecutive births from each centre was desirable to yield a sufficient number even of the commonest malformations to be of value for analysis. It was also realized that it would be unreasonable to ask the medical staff of busy maternity hospitals to continue the recording over a long period, perhaps more than two years, as changes of staff and diminishing interest in routine recording would be bound to interfere with efficiency. These limitations determined a search for hospitals or groups of hospitals which had a minimum of 10 000 births in two years. By European standards therefore these maternity hospitals would have to be rather large. There are relatively few University hospitals throughout the world of sufficient size and in countries in eastern Europe the "Mother and Child Institutes" usually have only about 100 beds and perhaps 2000 births per year. As will be seen from the data, these limitations resulted in some smaller series of recordings being arranged—on the principle that some data are better than none.

Large hospitals with so many births each year are inevitably very busy places and invariably are understaffed, so that it would have been unrealistic to expect recording of elaborate information about births. Further, uniform recording seemed essential. It was necessary, therefore, to decide what was the maximum amount of information which could reasonably be expected to be recorded in these hospitals which had the minimum facilities.

After consultations at the World Health Organization in Geneva with medical officers who had personal knowledge of many countries, letters were sent by the Organization to the Ministries of Health of a number of countries explaining what was proposed and asking for co-operation. Following this, a visit was paid to each country, except Australia, by a member of the staff of the Population Genetics Research Unit. It was not necessary to visit Australia as there were already close contacts with obstetricians in Melbourne and it was known that the system of recording there was very similar to that in the United Kingdom.

It proved possible in most, although not all, of the countries visited to find hospitals or groups of cooperating hospitals where there were sufficient numbers of births per year and where obstetricians and paediatricians were interested and willing to participate in a joint study. The centres at which recording was started and completed are listed at the front of this publication. In each case the name of the person directly responsible for the local arrangements is indicated, but it will be realized that there are many others—persons in Ministries of Health, obstetricians and paediatricians—whose co-operation was essential. It was made clear to the physicians at each centre visited that the data assembled belonged to them and could be published as desired. It was agreed that no publication of their findings would be made until they had seen the tabulated data from their own hospital and had given permission for their inclusion in a general report. The writers wish to make it clear that in presenting this report they are acting only as co-ordinating agents for many colleagues in all these centres.

Recording of births began at different times and its duration varied between centres. Completion of record forms began in the first centre in October 1961 and ended in the last centre in December 1964.

RECORDING, TRANSMISSION AND HANDLING OF DATA

The simple information which was recorded is shown in Annex 1. A 5-inch by 8-inch white card $(12.5 \text{ cm} \times 20.5 \text{-cm})$ was used for each single birth, and there were similar cards—yellow in colour with a place for the second member of a twin pair. or the second and third members of triplets on the front and back. These cards were printed in Oxford in English, Spanish, Serbo-Croat and Czech. They were serially numbered and then posted in batches to the various centres. Starting on a fixed date in each hospital every livebirth and stillbirth of over 28 weeks' duration of pregnancy was recorded. When completed, cards were returned in batches of one or two thousand to Oxford. The intention was that the cause of death and up to six malformations in each child would be coded and the whole information from each birth transferred to a punch card.

In practice the complexities of types of malformations and the difficulties of interpreting descriptions determined that the ultimate listing and sorting of malformations recorded were done by hand. Further, as might have been anticipated, no use could be made of the causes of death as recorded. As is well known, it is impossible to specify the underlying or the proximate causes of death in many perinatal deaths and the "causes" of death recorded reflected this difficulty.

The exceptions to the above system of recording were in Czechoslovakia and Northern Ireland. Dr V. Matousek, from the Biological Institute of the Czechoslovak Academy of Sciences, spent three weeks in this Unit prior to the study, familiarizing himself with the methodology of analysis which we were pursuing and, at the end of the period of recording, the paediatrician in charge, Dr J. Kucera, came to Oxford, bringing with him the information about all recorded malformations; these were listed in this Unit with his help. In this way a maximum degree of comparability could be achieved. The recording of the Northern Ireland data was started by one of us (A.C.S.) in 1957 when at Queen's University, Belfast. Although the recording system at Belfast was much more elaborate than that used in the present study, it was easy to take from the punched cards most of the information which was being collected in the other centres and it was felt that the inclusion of these data, which had been carefully collected over a number of years, was worth while.

In Oxford, the cards returned were hand-checked for discrepancies and omissions and, as far as possible, these were repaired by writing to the countries concerned. Once it had been confirmed that each card where the child was recorded as having a malformation (including "minor" malformations—considered below) had been correctly coded, the cards were sent for punching to the Statistical Section of this Unit. Thereafter the original cards of all children with malformations were returned to the main Unit for further consideration.

When a basic analysis of the data from each centre had been completed, 15 basic tables and lists

of malformations in a form previously agreed were sent out to each centre. The approval of the organizing physician was sought and he was asked to give permission for circulation of these tabulations to all the other centres.

Liaison was maintained with and between the centres by a series of bulletins which were sent out at intervals over the period of the study. These reported progress and called attention to difficulties being encountered in interpreting the returned cards, and were used to send out data and seek approval for the proposed form of their presentation.

ADMINISTRATIVE PROBLEMS

Inevitably, in dealing with so many centres in different parts of the world, many difficulties were encountered. Inexplicable postal delays in both directions were not uncommon whenever the package was of such a size that parcel post had to be employed and a customs declaration completed. Several outgoing batches of cards were returned for no apparent reason by customs authorities; others just never arrived. This was troublesome but could be remedied by dispatching further batches. More serious was the loss of many thousands of completed cards being returned to Oxford or the delay in whole or part of batches of boxes for many months. Several thousand cards sent by Dr Chow of the Kowloon Hospital never arrived, so that no data can be included from there. In addition some boxes from Santo Tomás Hospital, Panama, and from the Maternity Hospital, Kuala Lumpur, arrived too late to be included in the report. The date for final compilation of tables was repeatedly deferred in the hope that they might arrive but in the end the decision to proceed with assembly of the data could not further be delayed without serious disruption of the time-table of the work in this Unit.